(Pravastatin or Atorvastatin Evaluation and Infection Therapy) trial: "Intensive Versus Moderate Lipid Lowering With Statins After Acute Coronary Syndromes" (2). On the active debate regarding whether the appropriate treatment should be based on the dose of the statin or the achieved LDL, we agree that there have not been trials that directly compare 2 strategies of titrating to a specific LDL-C goal. All the trials use different, largely fixed regimens of a specific statin dose (either with intensive vs. moderate, or of statin therapy vs. placebo). In PROVE IT–TIMI-22, we designed the trial very specifically to have 2 different levels of achieved LDL-C so as to be able to compare patients who reached an average of <100 mg/dl, as recommended in the National Cholesterol Education Program (NCEP) III guidelines, versus a much lower LDL-C with a more intensive regimen, with the final median LDL-C values of 95 and 62 mg/dl, respectively.

Almost a decade ago, the NCEP Guideline committee adopted a practical approach to lipid lowering—where members specified target levels for LDL-C and other lipid levels. This was believed to be a means of having physicians identify high cholesterol values in patients and adjust treatment accordingly. The evidence directly supporting this approach does not exist, as recently lamented (3), but can be inferred from all the randomized trials.

For clinical care, we take a practical view. If we have a patient with an LDL <70 mg/dl on a moderate dose of a statin, we do not feel compelled to increase the dose. However, we are currently conducting the IMPROVE IT trial to address this question, to ascertain whether an even lower LDL is even better. It compares strategies using simvastatin versus simvastatin plus ezetimibe, which are anticipated to have achieved LDL levels of 65 versus 50 mg/dl, respectively. When the trial is completed in several years, we may have evidence to support an even lower target level for LDL.

For additional targets of therapy, we agree, and published the prospective analysis relating clinical event rates to levels of achieved C-reactive protein (4). We similarly have recently found triglycerides to be an important target for therapy (5). We agree that HDL is an important target as well, and we anticipate new approaches to address this important risk factor. All these data support the call for comprehensive management of all components of dyslipidemia.

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Depression and Heart Failure: Why the Link Continues to Elude Us

Rutledge et al.'s (1) important and comprehensive review of depression in heart failure highlights the relative neglect in investigating the key parameters of this important association in the literature. The researchers remind us there remains as yet no investigation of the effects of a depression intervention on objective clinical outcomes such as survival or secondary cardiac events in a heart failure (HF) population.

However, although their useful review emphasized the biological connections between HF and depression, some of the emerging key issues on the link between depression and heart disease possibly emphasize more the social and perceptual impacts of effect.

For example, we know that depression has a negative impact on social networks, and it could be that it partially mediates its effects on cardiovascular systems via this variable. It is now a well-established finding that those individuals who are more socially integrated—for example, in long-term relationships or connected to communities or organizations—display lower risks of premature all-cause mortality than do those who are not so well integrated socially (2).

Piferi and Lawler (2) have recently demonstrated that social support not only had a positive impact on blood pressure but *giving* social support appears to represent a separate construct from receiving social support and may exert a uniquely positive effect on health. It might be that future studies on depression and HF, particularly intervention ones, would need to take this kind of social mediating variable into account, and be highly specific as to whether giving or receiving social support was measured.

Another key aspect of depression, which should be part of the future of research into depression and HF, is the specific impact of low mood on perception. For example, Ruo et al. (3) recently established that depression has a clinically significant effect on self-rated health among women with coronary disease, even after adjustment for clinical diagnoses. The magnitude of this impact of depression on self-rated health was similar to that of major cardiovascular events such as angina, myocardial infarction, angioplasty, HF, or coronary bypass surgery.

Whether depressed individuals are less compliant with treatments and medical advice, and whether they are unlikely to attend follow-up, are recalcitrant over exercise, losing weight, improving diet, and quitting smoking remain open questions. Thus, the precise pathway via how their depression impacts on their physical health continues to be a mystery.

This gap in our current knowledge probably accounts for the recent failure to demonstrate a significant impact on physical outcomes for treating depression following myocardial infarction (4).

Future research efforts into HF and depression, as well as heart disease and psychological states in general, need to measure more precisely the multiplicity of impacts of depression on an individual in order to ultimately produce effective treatments. Currently, the field seems intent on importing the way we treat standard depression in psychiatry into the way depression should be approached in cardiology. It is highly unlikely this is going to help heart patients in the long run, as this would probably neglect the unique and various specific impacts of depression in heart disease and vice versa.

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Reply

Dr. Persaud offers several valuable comments concerning our recent review (1). The relationship between depression and heart failure (HF) is complex, and we fully agree that furthering our understanding of how these conditions interrelate will require the study of important psychosocial factors such as social support and social isolation in addition to biological mechanisms.

Although our review primarily focused on rates and prospective significance of depression in HF patients, we would like to use Dr. Persaud's comments as a platform to make several specific suggestions concerning applications to treatment.

First, treating and understanding depression's effects on HF patients begins at the stage of symptom recognition, a surprisingly difficult task. Depression is notoriously underrecognized in medical patients. The clinical presentations of HF and depression are often similar, complicating diagnosis and assessment of treatment benefits. Social stigmas against mental health diagnoses can make patients reluctant to acknowledge depressive symptoms. Depression may delay treatment-seeking behaviors in some, while increasing health care utilization in others. Depression symptoms can also vary widely across patients, and the meaning of these differences for HF is not known. Collectively, these factors undermine and may even argue against the application of standardized depression treatments in HF populations.

Second, efficacious treatments for depression are still lacking, despite the development of state-of-the-art pharmacotherapies. A substantial patient population does not respond and/or maintains clinically significant symptoms despite treatment attempts (2), and responsiveness may itself have prognostic importance (3).

Third, the presence of depression is not random; rather, it is disproportionately diagnosed among patients who are female, those suffering more advanced disease, those who are socially isolated, and those of lower socioeconomic status. These factors can affect patients' presenting symptoms, their ability or willingness to participate in treatment, their responsiveness to treatment, and their susceptibility to relapse.

Our review found the treatment literature for depression in HF to be poorly developed and methodologically inconsistent. At this early stage of research—and lacking any conclusive treatment evidence for survival or event outcomes from the much larger coronary artery disease literature—we believe it would be imprudent to call for clinical trials in HF at this time. Instead, we hope that our findings and insights from colleagues such as Dr. Persaud can be used to advance the treatment research in this area for potential future applications.

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